Asymmetric Synthesis Using Chirally Modified Borohydrides. Part 3.[1] Enantioselective Reduction of Ketones and Oxime Ethers with Reagents Prepared from Borane and Chiral Amino Alcohols

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The asymmetric reduction of aromatic and aliphatic ketones, halogeno ketones, hydroxy ketones, keto esters, and ketone oxime ethers with reagents prepared from borane and chiral amino alcohols has been investigated. When α,α-diphenyl-β-amino alcohols, such as (2*S*,3*R*)-(−)-2-amino-3-methyl-1,1-diphenylpentanol (**2d**), were used as a chiral auxiliary, very high enantioselectivities (*ca.* 90% e.e.) were obtained in the reduction of various ketones and oxime ethers.

In part 1 we reported that the asymmetric reduction of aromatic ketones with reagents prepared from chiral amino alcohols and borane gave optically active secondary alcohols with high enantioselectivity.[2] In our series of studies[1–4] on asymmetric reduction it has been found that the optically active α,α-diphenyl-β-amino alcohols, used as chiral auxiliaries were extremely effective reagents for asymmetric induction. Consequently, we have now extended the investigation to various compounds including aromatic ketones, aliphatic ketones, α-halogeno ketones, hydroxy ketones, keto esters, and ketone oxime ethers with the chiral reagents prepared from α,α-diphenyl-β-amino alcohols and borane. Most asymmetric reducing agents, even if they are effective for aromatic ketones, fail for the aliphatic ketones.[5a,b] However, our chiral reagent reduced aliphatic ketones as well as aromatic ones to optically active aliphatic alcohols with high enantioselectivity. Ketones having a further functional group such as α-halogeno ketones, *O*-protected hydroxy ketones, and keto esters were also found to be reduced chemoselectively to afford the optically active halohydrins, diols, and hydroxyesters, respectively. These are useful starting materials for the syntheses of other optically active compounds. The oxime ethers were reduced enantioselectively to the corresponding chiral secondary amines which are of importance for the preparation of synthetic drugs and resolving agents. We now report a simple procedure which achieves the reduction of various kinds of ketones and oxime ethers in optical purities approaching 100%.

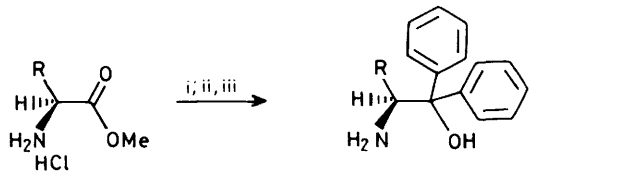
Results and Discussion

Asymmetric Reduction of Aromatic Ketones.—We have previously reported that the chiral reagent prepared from (*S*)-(−)-2-amino-3-methylbutan-1-ol [(*S*)-(**1**)] and borane in the molar ratio of 1:2 reduced 1-phenylbutan-1-one in tetrahydrofuran (THF) at 30 °C to (*R*)-1-phenylbutan-1-ol with 68% e.e.[2] Under the same reaction conditions a very high enantioselectivity (96% e.e.) was achieved with the chiral reagent from (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol [(*S*)-(**2**)], readily prepared in two steps from (*S*)-valine.[2] Of the various factors studied, the molar ratio of chiral amino alcohols and borane had the most dramatic effect. High stereoselectivity was always attained with the reagent prepared from a 1:2 molar ratio of amino alcohol and borane, whereas the reduction with the reagent with a 1:1 molar ratio resulted in a disappointingly low selectivity for various ketones.[2] Reduction with the 1:1 reagent of (*S*)-(**2b**)-borane also showed a similar trend (Table 1, run 6). Therefore, the reagents prepared from a 1:2 molar ratio of chiral amino alcohols and borane were used in the following unless otherwise stated. Aromatic ketones examined were all thus reduced asymmetrically in a highly stereoselective manner, giving 94—100% optical yields in each case. The asymmetric reduction of aromatic ketones all showed a marked im-

Table 1. Asymmetric reduction of aromatic ketones with the reagent prepared from chiral amino alcohols and borane in THF at 30 °C. The yield of alcohol was 100% in each case[a]

			Alcohol produced		
Run	Amino alcohol	Ketone	$[\alpha]_D$/°	Optical yield (%)	Absolute config.
1	(*S*)-(**1**)	MeCOPh	+25.7[d]	49	*R*
2	(*S*)-(**2b**)	MeCOPh	+49.1	94	*R*
3	(*S*)-(**2b**)	EtCOPh	+44.2[e]	94	*R*
4	(*S*)-(**2b**)	Pr^{n}COPh	+43.4[f]	96	*R*
5[b]	(*S*)-(**2b**)	Pr^{n}COPh	+42.9	95	*R*
6[c]	(*S*)-(**2b**)	Pr^{n}COPh	+3.00	6.6	*R*
7	(*R*)-(**2b**)	Pr^{n}COPh	−41.3	91 (97)[g]	*S*
8	(*S*)-(**2b**)	Bu^{n}COPh	+20.0[h]	100	*R*

[a] Based on relative g.l.c. peak areas of alcohol and ketone. [b] Recovered (*S*)-(**2b**) was used. [c] The reagent prepared from (*S*)-(**2b**) and borane in a 1:1 molar ratio was used. [d] In CH_2Cl_2 (U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701). [e] In acetone (H. Kwart and D. P. Hoster, *J. Org. Chem.*, 1967, **32**, 1867). [f] In benzene (R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem. Soc.*, 1979, **101**, 3129). [g] Optical yield corrected for the optical purity of the (*R*)-(**2b**) (94% e.e., see Experimental section). [h] Neat (A. Horeau, J. P. Guette, and R. Weiolmann, *Bull. Soc. Chim. Fr.*, 1966, 3513).



2a; R = Me
b; R = MePr^i
c; R = MeCH$_2$Pr^i
d; R = Bu^s
e; R = −CH$_2$Ph
f; R = −CH$_2$CH$_2$SMe
g; R = −CH$_2$C$_6$H$_4$OCH$_2$Ph

Scheme. *Reagents:* i, PhMgBr; ii, 2M-HCl; iii, NH_4OH.

Table 2. Asymmetric reduction of aliphatic ketones with the reagent prepared from (*S*)-(**2b**) and borane in THF at 30 °C. The yield of alcohol was 100% in each case

		Alcohol produced		
Run	Ketone	$[\alpha]_D$/°	Optical yield (%)	Absolute config.
1	Bu^{n}COMe	−6.73[d]	55	*R*
2	Pentyl^{n}COMe	−6.36[e]	56	*R*
3	Hexyl^{n}COMe	−5.86[f]	58	*R*
4	Pr^{i}COMe	−3.21[g]	60	*R*
5	Bu^{i}COMe	−12.48[h]	61	*R*
6	Bu^{t}COMe	−5.98[i]	73	*R*
7[a]	Bu^{t}COMe	−3.57	44	*R*
8[b]	Bu^{t}COMe	−6.32	78	*R*
9[c]	Bu^{t}COMe	−6.40	79	*R*

[a] (*S*)-(**1**) was used. [b] Reaction carried out at 0 °C. [c] Reaction carried out at −78 °C. [d] Neat (R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1911, **99**, 45). [e] In ethanol ('Dictionary of Organic Compounds', J. Buckingham, ed., 5th edn., Chapman and Hall, New York, 1982, vol. 3). [f] In ethanol (R. K. Hill, *J. Am. Chem. Soc.*, 1958, **80**, 1511). [g] Neat (R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1913, **103**, 1957). [h] Neat (P. A. Levene and A. Rothen. *J. Org. Chem.*, 1936, **1**, 76). [i] Neat (P. Newman, P. Lutkin, and K. Mislow, *J. Am. Chem. Soc.*, 1958, **80**, 465).

Table 3. Asymmetric reduction of 3,3-dimethylbutan-2-one and acetophenone with the reagent prepared from various chiral amino alcohols and borane in THF at 30 °C. The yield of alcohol was 100% in each case

		3,3-Dimethylbutan-2-ol		1-Phenylethanol	
Run	Amino alcohol	$[\alpha]_D$[a,b]/°	Optical yield (%)	$[\alpha]_D$[b,c]/°	Optical yield (%)
1	(*S*)-(**1**)	−3.57	44	+25.73	49
2	(**2a**)	−5.83	72	+44.63	85
3	(**2b**)	−5.98	74	+49.10	94
4	(**2c**)	−4.46	55	+43.11	82
5	(**2d**)	−7.21	89	+49.88	95
6	(**2e**)	−6.72	83	+45.67	87
7	(**2f**)	−5.02	65	+35.13	67

[a] Neat (P. Newmann, P. Lutkin, and K. Mislow, *J. Am. Chem. Soc.*, 1958, **80**, 465). [b] All absolute configurations were *R*. [c] In CH_2Cl_2 (U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701).

Table 4. Effect of formation temperature of (**2d**)-borane reagent on optical yield in the asymmetric reduction of 3,3-dimethylbutan-2-one in THF. The yield of butanol was 100% in each case

		3,3-Dimethylbutan-2-ol		
Run	Temp. (°C)	$[\alpha]_D$[a]/°	Optical yield (%)	Absolute config.
1	30	−6.64	82	*R*
2	0	−7.78	96	*R*
3	−78	−7.21	89	*R*

[a] Neat (P. Newman, P. Lutkin, and K. Mislow, *J. Am. Chem. Soc.*, 1958, **80**, 465).

provement in optical yield with the above reagent compared with (*S*)-(**1**)-borane reagent as shown in Table 1 (runs 1 and 2). The steric bulkiness of the two phenyl groups of (**2b**) may control the reduction course effectively. The chiral reagent from (*S*)-(**2b**) gives the (*R*)-alcohol while the reversed stereoselectivity with the same degree of asymmetric induction was achieved by the use of the reagent from (*R*)-(**2b**). Since both (*S*)- and (*R*)-(**2b**) are readily accessible, this method allows both enantiomers of secondary alcohols to be synthesized readily from aromatic ketones. Insolubility of the hydrochloride of (*S*)- or (*R*)-(**2b**) either in water or in organic solvents made separation of the product from the chiral auxiliary easy. In fact (**2b**) was recovered in over 80% yield without any loss of optical purity. Both optical and chemical yields were reproducible when the reagent from the recovered (*S*)-(**3b**) and borane was used (Table 1, runs 4 and 5).

Asymmetric Reduction of Aliphatic Ketones.—Most asymmetric reducing agents even if they are highly effective for aromatic ketones fail for the aliphatic ketones. For example, the chiral binaphthyl-$LiAlH_4$[5a] and chiral diamine-$LiAlH_4$[5b] reagents, which are highly effective for aromatic ketones, reduced octan-2-one in only 24% e.e. and 26% e.e., respectively. Several other chirally modified reducing agents[6a–c] examined for the asymmetric reduction of aliphatic ketones all gave optical yields below 50% e.e. Recently, M. M. Midland *et al.* reported that the asymmetric reduction of octan-2-one with NB–Enantride at −78 °C gave (*S*)-octan-2-ol in 79% e.e. which is the highest value so far reported for aliphatic alcohols.[7] Asymmetric reduction of aliphatic ketones with the reagent from (**2b**) and borane produced a high degree of enantioselectivity with various aliphatic ketones as shown in Table 2. Since fairly good enantioselectivities were obtained even in the reduction of straight chain aliphatic ketones, it is clear that our reagent has the ability to distinguish between small differences in the steric size of alkyl groups on the two sides of the carbonyl group of such compounds. The enantioselectivity of the present reagent clearly reflects the order of steric bulkiness of the alkyl chain. Reduction of 3,3-dimethylbutan-2-one (pinacoline) yielded (*R*)-3,3-dimethylbutan-2-ol in 73% e.e.; at 30 °C or −78 °C it resulted in somewhat better enantioselectivities (78 and 79% e.e.; respectively).

Other Optically Active Amino Alcohols.—From the results of the asymmetric reduction of aromatic and aliphatic ketones, (**2b**) was found to be a very effective chiral auxiliary. Other optically active amino alcohols having the similar structure were easily prepared from naturally occurring amino acids by using a procedure similar to that of (**2b**), as shown in the Scheme. Acetophenone and pinacoline were reduced with the reagents from those chiral amino alcohols containing a diphenyl group. Results are summarized in Table 3. A high degree of enantioselectivity was achieved by the use of the reagent from 2-(*S*)-3-(*R*)-(−)-2-amino-3-methyl-1,1-diphenylpentan-1-ol (**2d**) on either aromatic or aliphatic ketones (Table 3, run 5). In addition to various other factors affecting the enantioselectivity, it was found that the optical yield was also influenced by the procedure for preparing the chiral reducing agent. When 2 mol of borane were added to (**2d**) at −78 °C, 89% enantioselectivity was attained in the reduction of pinacoline, while the reverse addition of (**2d**) to 2 mol of borane gave a somewhat lower selectivity (77% e.e.). If instead of 2 mol of borane, 1 mol of borane and 1 mol of boron trifluoride were added a disappointingly low level of enantioselectivity (10% e.e.) was achieved. It was confirmed again here that addition of 2 mol of borane to the chiral amino alcohol was necessary for a high % e.e. It was found that the temperature during addition of borane to (**2d**) was also an important factor as shown in Table 4. Interestingly, at 0 °C the reagent prepared from borane and (**2d**) reduced pinacoline to 3,3-dimethylbutan-2-ol with 96% e.e.

Table 5. Asymmetric reduction of α-halogeno ketones with the reagent prepared from (**2d**) and borane and preparation of optically active epoxides. The yield of halohydrin and epoxide was 100% in each case

		Halohydrin produced			Epoxide produced		
Run	α-Halogeno ketone	$[\alpha]_D$/°	Optical yield (%)	Absolute config.	$[\alpha]_D$/°	Optical yield (%)	Absolute config.
1	$PhCOCH_2Cl$	+46.20[a]	96	*S*	−33.07[c]	96	*S*
2	$PhCOCH_2Br$	+32.41[b]	83	*S*	−28.75	83	*S*
3	Bu^tCOCH_2Cl				+14.95[d]	90	*S*
4	Bu^tCOCH_2Br				+15.40	93	*S*

[a] In cyclohexane (L. C. J. van der Lean, J. B. N. Engberts, and T. J. de Boer, *Tetrahedron*, 1971, **27**, 4323). [b] In $CHCl_3$ (M. Imuta, K. Kawai, and H. Ziffer, *J. Org. Chem.*, 1980, **45**, 3352). [c] Neat (G. Berti, F. Bottari, P. L. Ferrarini, and B. Macchia, *J. Org. Chem.*, 1965, **30**, 4091). [d] Neat (M. Sepulchre and A. M. Sepulchre, *Bull. Soc. Chim. Fr.*, 1973, 1164).

Table 6. Effect of formation temperature of (**2d**)-borane complex on optical yield in the asymmetric reduction of 1-chloroacetophenone. The yield of the chlorohydrin was 100% in each case

		2-Chloro-1-phenylethanol		
Run	Temp. (°C)	$[\alpha]_D$[a]/°	Optical yield (%)	Absolute config.
1	30	+41.40	86	*S*
2	0	+46.18	96	*S*
3	−78	+44.25	92	*S*

[a] In cyclohexane (L. C. J. van der Lean, J. B. N. Engberts, and T. J. de Boer, *Tetrahedron*, 1971, **27**, 4323).

Table 7. Asymmetric reduction of prochiral ketones containing functional group with (**3d**)-borane reagent in THF at 30 °C. The yield of alcohol was 100% in each case

			Alcohol produced		
Run	Ketone	Product	$[\alpha]_D$/°	Optical yield (%)	Absolute config.
1[a]	$PhCOCH_2OH$	$PhCH(OH)CH_2OH$	−6.15[b]	15	*R*
2	$PhCOCH_2OSiMe_3$	$PhCH(OH)CH_2OH$	+30.90	80	*S*
3	$PhCOCH_2OCOMe$	$PhCH(OH)CH_2OH$	+23.61	58	*S*
4	PhCOCOOMe	PhCH(OH)COOMe	+44.10[c]	25	*S*

[a] 0.5 Equiv. of the hydroxy ketone was used. [b] In ethanol (V. Prelog, M. Wilhelm, and D. B. Bright, *Helv. Chim. Acta*, 1954, **37**, 221). [c] In chloroform (C. E. Wood, J. E. Such, and F. Scart, *J. Chem. Soc.*, 1926, 1928).

Under the same reaction conditions, the aromatic ketone (acetophenone) was reduced with 97% e.e.

Asymmetric Reduction of Ketones Containing Functional Groups with the Reagent from (**2d**) *and Borane.*—In order to extend this method of asymmetric reduction to the ketones containing a different functional group, α-halogeno ketones, keto esters, and hydroxy ketones were examined by the chiral reagent prepared from (**2d**) and borane, having enzyme-like selectivity for ketones. Asymmetric reduction of α-halogeno ketones produced optically active halohydrins, readily transformed into the epoxides. Since the epoxide unit provides a convenient handle for further elaborations the resulting chiral epoxides are very useful in organic synthesis. Reduction of α-chloroacetophenone went to completion in 1 h at 30 °C with high chemo- and enantio-selectivity (96% e.e.) (Table 5). The isolated chlorohydrin was easily converted into (*S*)-styrene oxide with no racemization. With the sterically more hindered bromohydrin the enantioselectivity was lower. The temperature of formation of the chiral amino alcohol–borane complex influenced the optical yield of halohydrin (Table 6). Ketones with their hydroxy group protected by trimethylsily ether were also reduced with high enantioselectivity (80% e.e.) under the same conditions (Table 7). Asymmetric reduction of the same ketone with the hydroxy group protected as an acetate gave lower selectivity (58% e.e.). The reduction of methyl benzoylformate showed low selectivity (25% e.e.) because of the enhanced reactivity of the keto carbonyl group by the adjacent ester group together with the bulkiness of the latter. Brown *et al.*[8] reported that although neat *B*-pinan-3-yl-9-borabicyclo-[3.3.1]nonane (Midland's reagent) reduced 1-halogeno ketones to (*R*)-halohydrins with high enantioselectivities (35—95% e.e.), long reaction times (2—45 days) were needed to give high chemical yields. The same reagent also reduced 1-keto esters to give chiral 1-hydroxy esters with high selectivities (80—100% e.e.).[9]

Asymmetric Reduction of Oxime Ethers.—Landor *et al.*[10] have studied the preparation of optically active amines by asymmetric reduction of the prochiral ketone oximes with $LiAlH_4$–3-*O*-cyclohexyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex. Thus, cyclohexyl methyl ketone oxime was reduced to an optically active 1-cyclohexylethylamine with an optical purity of up to 52%, the highest value so far reported for the asymmetric hydride reduction of a compound containing a C=N bond. Acetophenone *O*-benzyloxime when treated with the (**2d**)-borane reagent under similar conditions to those used for the ketone reductions gave optically active 1-phenylethylamine with high enantioselectivity (91% e.e.) (Table 8); use of (**2g**) improved the selectivity (94% e.e.). Complete reduction required 24 h, a result of a decreased reaction rate arising from co-ordination between the oxime ether lone pair of electrons and boron. Addition of a Lewis acid ($AlCl_3$) to the oxime ether before the reaction overcame this problem, and complete reduction occurred in 3 h with 89% e.e. (Table 8, run 5). Table 9 shows the effect of *O*-substituents on the optical yield of chiral 1-

Table 8. Asymmetric reduction of acetophenone *O*-benzyloxime with the reagent prepared from chiral amino alcohols and borane in THF at 30 °C. The yield of the amine was 100% in each case

		1-Phenylethylamine		
Run	Amino alcohol	$[\alpha]_D$[a]/°	Optical yield (%)	Absolute config.
1	(*S*)-(**1**)	−25.29	87	*S*
2	(**2b**)	−26.25	91	*S*
3	(**2d**)	−26.43	91	*S*
4	(**2g**)	−27.30	94	*S*
5[b]	(**2g**)	−25.83	89	*S*

[a] In methanol (W. Leithe, *Ber.*, 1931, **64**, 2827). [b] Equimolar $AlCl_3$ was added to the oxime ether before the reaction.

Table 9. Asymmetric reduction of acetophenone *O*-alkyloxime with (**2b**)-borane reagent in THF at 30 °C. The yield of the amine was 100% in each case

		1-Phenylethylamine		
Run	Ph(Me)C=NOR	$[\alpha]_D$[a]/°	Optical yield (%)	Absolute config.
1	H	−0.18	0.6	*S*
2	Me	−28.72	99	*S*
3	Et	−23.26	81	*S*
4	CH_2Ph	−26.24	91	*S*
5	$SiMe_3$	−18.01	62	*S*
6	COMe	+2.51	8.7	*R*

[a] In methanol (W. Leithe, *Ber.*, 1931, **64**, 2827).

Table 10. Asymmetric reduction of several ketone *O*-methyloximes with (**2b**)-borane reagent in THF at 30 °C. The yield of the primary amine was 100% in each case

			Amine produced		
	R^1R^2C=NOMe				
Run	R^1	R^2	$[\alpha]_D$/°	Optical yield (%)	Absolute config.
1	Ph	Me	−28.72[a]	99	*S*
2	Naphthyl	1-Me	−56.60[b]	70	*S*
3	Naphthyl	2-Me	−26.13[c]	*e*	*S*[f]
4	1-Tetralone		+29.20[d]	69	*S*[f]

[a] In methanol (W. Leithe, *Ber.*, 1931, **64**, 2827). [b] Neat (H. Wolf, E. Bunnenberg, and C. Djerassi, *Chem. Ber.*, 1964, **97**, 533). [c] In ethanol (A. Fredga, B. Sjoberg, and R. Sanberg, *Acta Chem. Scand.*, 1957, **11**, 1609). [d] Neat (V. Ghishlandi and D. Vercesi, *Farmaco Ed. Sci.*, 1971, **26**, 474). [e] Reported optical rotation is $[\alpha]_D$ ±19° (in ethanol). [f] *S* Notation predicted from the related absolute configuration of the other products.

phenylethylamine. The bulky trimethylsilyl group lowered selectivity while asymmetric reduction of the methyl ether was most efficient. Although the reduction of acetate gave only a low selectivity, (*R*)-amine was obtained in excess. The other oxime methyl ethers are summarized in Table 10.

Conclusions

Aromatic and aliphatic ketones, ketones having functional groups, and oxime ethers undergo asymmetric reduction with the reagent prepared from a chiral amino alcohol [such as (**2d**)], and borane, in high chemical yield and with a high degree of enantioselectivity. Although the mechanism by which this asymmetric reduction occurs is unclear, it is probably connected with differences in steric bulk in the path of the approaching substrate.

Experimental

N.m.r. spectra were taken on a JEOL JNM-PMX 60 (60 MHz) spectrometer. I.r. spectra were measured with a JASCO A-3 instrument for Nujol mulls. M.p.s were determined using a Yanagimoto micro melting point apparatus. G.l.c. was performed on a Yanaco G180 instrument with a stainless-steel analytical column (3 m × 3 m) packed with PEG 20M on Diasolid L. The ratios of alcohol:unchanged ketone were determined by peak areas. Optical rotations were taken on a JASCO DIP-140 digital polarimeter using a 1 cm or a 10 cm thermostatted microcell. T.l.c. was run on silica gel 60F-254 pre-coated plates with benzene–ethyl acetate (9:1 v/v) or chloroform as the mobile phase.

All reactions were carried out under a nitrogen atmosphere. THF was dried over sodium wire and distilled over $LiAlH_4$ immediately before use. $AlCl_3$ was dried *in vacuo* for 5 h at 80 °C prior to use. Aromatic and aliphatic ketones were all dried and distilled over calcium hydride. Borane–THF was prepared by reaction of sodium borohydride with boron trifluoride–ether complex according to the procedure of Brown.[11]

2-Chloroacetophenone and 2-bromoacetophenone (Tokyo Kasei Co.) were recrystallized from carbon tetrachloride and methanol, respectively. 1-Chloro-3,3-dimethylbutan-2-one[12] was prepared from 3,3-dimethylbutan-2-one with chlorine by the method of Newman, Farbman, and Hipsher[13] and purified by fractional distillation, b.p. 85 °C/30 mmHg, δ($CDCl_3$) 4.30 (2 H, s, CH_2) and 1.16 (9 H, s, CMe_3).

1-Bromo-3,3-dimethylbutan-2-one[14] was prepared by a similar method and purified by fractional distillation, b.p. 105 °C/60 mmHg, δ_H($CDCl_3$) 4.08 (2 H, s, CH_2) and 1.16 (9 H, s, CMe_3).

Preparation of Ketones containing Functional Groups.—2-Hydroxyacetophenone was prepared by the reaction between 2-bromoacetophenone and potassium formate, followed by hydrolysis of the ester with methanol and purified by recrystallization from ethyl acetate–hexane, m.p. 88 °C; δ($CDCl_3$) 7.95—7.10 (5 H, m, ArH), 4.70 (2 H, s, CH_2) and 3.37 (1 H, s, OH) (Found: C, 70.5; H, 5.95. $C_8H_8O_2$ requires C, 70.6; H, 5.9%).

Trimethylsilyl chloride (6.9 g) in dry THF (20 ml) was added slowly to the solution of 2-hydroxyacetophenone (6.8 g) in dry THF (50 ml) in the presence of triethylamine (5.6 g) at 0 °C. The solution was stirred at room temperature for 8 h. Filtration and evaporation of the solvent followed by distillation gave 2-trimethylsilyloxyacetophenone (8.3 g), b.p. 115 °C/4 mmHg; δ($CDCl_3$) 7.80—6.90 (5 H, m, ArH), 4.72 (2 H, s, CH_2), and 0.00 (9 H, s, $SiMe_3$) (Found: C, 63.6; H, 7.7. $C_{11}H_{16}O_2Si$ requires C, 63.4; H, 7.7%).

Acetyl chloride (4.9 g) was added slowly to the solution of 2-hydroxyacetophenone (7.7 g) in pyridine (30 ml) at −10 °C; this was stirred at 0 °C for 3 h and then poured into 2M-HCl–ice. The solution was extracted with ether and dried ($MgSO_4$). Distillation gave the 2-acetoxyacetophenone (7.2 g), b.p. 170—175 °C/1 mmHg; δ($CDCl_3$) 7.95—7.20, (5 H, m, ArH), 5.21 (2 H, s, CH_2), and 2.32 (3 H, s, Me) (Found: C, 67.5; H, 5.6. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%).

Preparation of Ketone Oxime Ethers.—Ketone oximes were prepared by standard methods[15] and were purified by recrystallization. N.m.r. measurements showed that all were in *anti*-form. Ketone *O*-alkyloximes were prepared by the methods of Karabatsos and Hsi[15] and Corey *et al.*[16] and purified by fractional distillation.

Acetophenone O-Benzyloxime.—To a suspension of NaH (2.9 g) in 50 ml of dry *N*,*N*-dimethylformamide (DMF) at 0 °C was added a solution of acetophenone oxime (13.5 g) in dry DMF

(100 ml). The reaction mixture was stirred for 1 h at 0 °C and benzyl chloride (13.8 ml) was added. The ice-bath was removed and the reaction mixture stirred for an additional 5 h. After removal of DMF under reduced pressure the residue was taken up in ether (3 × 75 ml) and washed with 50% saturated brine. The combined organic layers were dried ($MgSO_4$) and evaporated to furnish a colourless oil, which was distilled to give the oxime ether (16.8 g), b.p. 145 °C/5 mmHg; δ($CDCl_3$) 7.80—7.00 (10 H, m, ArH), 5.16 (2 H, s, CH_2), and 2.16 (3 H, s, Me) (Found: C, 79.9; H, 6.8; N, 6.3. $C_{15}H_{15}NO$ requires C, 80.0; H, 6.7; N, 6.2%).

Other oxime ethers were prepared similarly.

Acetophenone O-*methyloxime*.[15] B.p. 89 °C/5 mmHg; δ($CDCl_3$) 7.75—6.95 (5 H, m, ArH), 4.00 (3 H, s, OMe) and 2.16 (3 H, s, Me).

Acetophenone O-*ethyloxime*. B.p. 78 °C/4 mmHg; δ($CDCl_3$) 7.78—7.00 (5 H, m, ArH), 4.20 (2 H, q, CH_2), 2.16 (3 H, s, N=CMe), and 1.33 (3 H, t, CH_2Me) (Found: C, 73.4; H, 8.1; N, 8.5. $C_{10}H_{13}NO$ requires C, 73.6; H, 8.0; N, 8.6%).

Acetophenone O-*trimethylsilyloxime*. B.p. 105 °C/2 mmHg; δ($CDCl_3$) 7.78—6.90 (5 H, m, ArH), 2.31 (3 H, s, Me), and 0.00 (9 H, s, $SiMe_3$) (Found: C, 63.6; H, 8.2; N. 6.7. $C_{11}H_{17}NOSi$ requires C, 63.7; H, 8.3; N, 6.8%).

Methyl 1-*naphthyl ketone* O-*methyloxime*. B.p. 132 °C/3 mmHg; δ($CDCl_3$) 8.00—7.30 (7 H, m, ArH), 4.00 (3 H, s, OMe), and 2.33 (3 H, s, Me) (Found: C, 78.4; H, 6.5; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%).

2-*Naphthyl methyl ketone* O-*methyloxime*. M.p. 92 °C; δ($CDCl_3$) 8.00—7.13 (7 H, m, ArH), 4.00 (3 H, s, OMe), and 2.33 (3 H, s, Me) (Found: C, 78.4; H, 6.6; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%).

3,4-*Dihydronaphthalen*-1(2H)-*one* O-*methyloxime*. B.p. 114 °C/2 mmHg; δ($CDCl_3$) 7.75—6.85 (4 H, m, ArH), 3.87 (3 H, s, Me), 2.63 (2 H, t, CH_2), 2.58 (2 H, t, CH_2), and 1.73 [2 H, (pent, $CH_2CH_2CH_2$)] (Found: C, 75.3; H, 7.4; N, 8.0. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%).

Acetophenone O-*Acetoxyoxime*.—Acetyl chloride (4.7 g) was added dropwise to a solution of acetophenone oxime (6.8 g) in pyridine (50 ml) at −10 °C and the mixture stirred at 0 °C for 1 h; it was then poured into 2M-HCl–ice. The precipitate was filtered off, washed with cold water, and recrystallized from CCl_4–light petroleum: m.p. 50 °C; δ($CDCl_3$) 7.70—7.00 (5 H, m, ArH), 2.26 (3 H, s, Me), and 2.10 (3 H, s, COMe) (Found: C, 67.9; H, 6.2; N, 7.9. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%).

(S)-(+)-2-*Amino*-3-*methylbutan*-1-*ol*, (S)-(**1**).—This compound, prepared by the reduction of (*S*)-valine (from Nihon Rika Yakuhin Co.) with $LiAlH_4$ according to the procedure reported in Part 1[2] of this series, had b.p. 55—57 °C/2 mmHg, $[\alpha]_D^{25}$ +18.41° (*c*, 2.01 in ethanol) {lit.,[17] $[\alpha]_D^{25}$ +18.5° (*c*, 7.83 in ethanol)}.

(S)-(−)-2-*Amino*-3-*methyl*-1,1-*diphenylbutanol*, (S)-(**2b**).—This compound was prepared from (*S*)-valine methyl ester hydrochloride with an 8-fold excess of phenylmagnesium bromide in THF at 0—10 °C for 5 h. After work-up, (*S*)-(**2b**) was obtained in 56% yield, m.p. 94—95 °C, $[\alpha]_D^{25}$ −127.7° (*c*, 0.639 in $CHCl_3$); δ($CDCl_3$) 7.70—6.85 (10 H, m, ArH) 4.10 (1 H, m), 3.70 (1 H, d), 1.70 (1 H, m), and 0.82 (6 H, dd) (Found: C, 80.3; H, 8.3; N, 5.7. $C_{17}H_{21}NO$ requires C, 80.0; H, 8.7; N, 5.5%).

(R)-(+)-2-*Amino*-3-*methyl*-1,1-*diphenylbutanol*, (R)-**2b**.—This compound was similarly obtained in 52% yield from the methyl ester hydrochloride of (*R*)-valine (93.4% optical purity, supplied by Kyowa Hakko Co.) with an excess of phenylmagnesium bromide, m.p. 94—95 °C, $[\alpha]_D^{25}$ +120.2° (*c*, 0.272, $CHCl_3$); δ($CDCl_3$) 7.70—6.85 (10 H, m), 4.10 (1 H, m), 3.70 (1 H, d), 1.70 (1 H, m), and 0.82 (6 H, dd) (Found: C, 80.5; H, 8.5; N, 5.7. $C_{17}H_{21}NO$ requires C, 80.0; H, 8.7; N, 5.5%).

Similarly, other chiral amino alcohols employed in this study were prepared in 40—60% yield by the reaction of the corresponding α-amino acid methyl ester hydrochloride with an excess of phenylmagnesium bromide in THF at 0—10 °C for 5—8 h, followed by recrystallization.

(S)-(−)-2-*Amino*-1,1-*diphenylpropanol* (**2a**), m.p. 100—102 °C, $[\alpha]_D^{25}$ −82.38° (*c*, 0.814 in $CHCl_3$), {lit.,[18] $[\alpha]_D^{25}$ −82.3° (*c*, 1.6776 in $CHCl_3$)}.

(S)-(−)-2-*Amino*-4-*methyl*-1,1-*diphenylpentanol* (**2c**), m.p. 132—134 °C, $[\alpha]_D^{25}$ −95.12° (*c*, 1.006 in $CHCl_3$); δ($CDCl_3$) 7.70—7.00 (10 H, m), 3.93 (1 H, m), 1.48 (2 H, m), 1.33—1.00 (3 H, m), and 0.87 (6 H, d) (Found: C, 80.2; H, 8.7; N, 5.3. $C_{18}H_{23}NO$ requires C, 80.3; H, 8.6; N, 5.2%).

(2S, 3R)-(−)-2-*Amino*-3-*methyl*-1,1-*diphenylpentanol* (**2d**), m.p. 135—136 °C, $[\alpha]_D^{25}$ −124.10° (*c*, 1.232 in $CHCl_3$); δ($CDCl_3$) 7.90—6.62 (10 H, m), 3.83 (1 H, d), 2.18 (2 H, m), and 1.95—0.68 (9 H, m) (Found: C, 79.8; H, 8.6; N, 5.3. $C_{18}H_{23}NO$ requires C, 80.3; H, 8.6; N, 5.2%).

(S)-(−)-2-*Amino*(1,1,3-*triphenylpropanol* (**2e**), m.p. 144—145 °C, $[\alpha]_D^{25}$ −88.50° (*c*, 0.604 in $CHCl_3$) δ($CDCl_3$) 7.83—7.22 (10 H, m), 7.22 (5 H, s), 4.18 (1 H, dd), 2.60 (2 H, dd), and 1.13 (2 H, m) (Found: C, 83.0; H, 6.9; N, 4.5. $C_{21}H_{21}NO$ requires C, 83.1; H, 7.0; N, 4.6%).

(S)-(−)-2-*Amino*-4-*methylthio*-1,1-*diphenylbutanol* (**2f**), m.p. 96—98 °C, $[\alpha]_D^{25}$ −108.57° (*c*, 0.986 in $CHCl_3$); δ($CDCl_3$) 7.57—6.80 (10 H, m), 2.97 (1 H, m), 2.42 (2 H, t), 1.83 (3 H, s), 1.52 (2 H, m), and 1.22 (2 H, m) (Found: C, 70.6; H, 7.3; N, 4.9; S, 11.5. $C_{17}H_{21}NOS$ requires C, 71.0; H, 7.4; N, 4.9; S, 11.2%).

(S)-(−)-2-*Amino*-3-(p-*benzyloxy*)*phenyl*-1,1-*diphenylpropanol* (**2g**), m.p. 136—137 °C, $[\alpha]_D^{25}$ −51.71° (*c*, 1.534 in THF); δ($CDCl_3$) 7.60—6.53 (19 H, m) 4.84 (2 H, s), 3.93 (1 H, dd), 2.29 (2 H, d), and 1.00 (2 H, m) (Found: C, 82.4; H, 6.7; N, 3.5. $C_{28}H_{27}NO_2$ requires C, 82.1; H, 6.7; N, 3.4.%).

Asymmetric Reduction of Acetophenone with the (**2**)·*Borane Reagent*.—A solution of borane (20 mmol) in THF (10 ml) was added dropwise to a solution of (*S*)-(**2b**) (10 mmol) at −78 °C during *ca.* 20 min. The resulting solution was gradually warmed to 0 °C and stirring continued at 0 °C for 8 h; a solution of acetophenone (8 mmol) in THF (5 ml) was then added dropwise during 5 min. The resulting mixture was stirred at 30 °C for 2 h and then decomposed by the addition of 2M-HCl. After hydrolysis, evaporation of THF deposited the (*S*)-(**2b**)·HCl as a white solid which was collected on a glass filter and washed with ether. The ether extract was dried ($MgSO_4$) and evaporated to give a colourless oil which upon distillation (bulb-to-bulb) furnished 1-phenylethanol (0.88 g, 90% of isolated material); this was characterized by i.r. and n.m.r. spectroscopy and shown to be homogeneous by t.l.c. and g.l.c. analyses. The optical rotations were $[\alpha]_D^{25}$ +49.10° (*c*, 3.54 in CH_2Cl_2) and $[\alpha]_D^{25}$ +41.00° (neat) {lit.,[19] $[\alpha]_D^{23}$ −52.5° (*c*, 2.27 in CH_2Cl_2), lit.,[20] $[\alpha]_D^{25}$ +43.6° (neat)}.

A number of other asymmetric reductions using different reagents and ketones were performed under conditions similar to those described above.

Preparation of an Optically Active Epoxide.—Optically active styrene chlorohydrin obtained from asymmetric reduction of α-chloroacetophenone with (**2b**)–borane reagent $[\alpha]_D^{25}$ +46.20° (*c*, 2.35 in cyclohexane), 96% e.e., (1.1 g, 7 mmol) in ether (10 ml) was treated with 2M-NaOH (10 ml) at 0 °C for 3 h to give optically active styrene oxide, $[\alpha]_D^{25}$ −42.65° (*c*, 3.82 in benzene), 96% e.e.

Asymmetric Reduction of Ketone Oxime Ethers with the (S)-(**2b**)·*Borane Reagent*.—A solution of borane (20 mmol) in THF

(10 ml) was added dropwise to a stirred solution of (*S*)-(**2b**) (10 mmol) in THF (10 ml) at 0 °C during *ca.* 20 min. The resulting solution was stirred at 0 °C for 8 h and then a solution of acetophenone *O*-benzyloxime (1.8 g, 8 mmol) in THF (5 ml) was added dropwise during 5 min. The resulting mixture was stirred at 30 °C for 24 h and then decomposed by the addition of 2M-HCl. After hydrolysis, evaporation of THF deposited the (*S*)-(**2b**)·HCl as a white solid, which was collected on a glass filter and washed with water. The aqueous acid extract was shaken with ether, cooled, basified with ammonium hydroxide, and extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated to give a colourless oil which upon distillation (bulb-to-bulb) furnished 1-phenylethylamine; this was characterized by i.r. and n.m.r. spectroscopy and shown to be homogeneous by t.l.c. and g.l.c. analyses. The optical rotations were $[\alpha]_D^{20}$ −26.24° (*c*, 4.10 in methanol) and $[\alpha]_D^{22}$ −36.68° (neat) {lit.,[21] $[\alpha]_D^{20}$ −29° (in methanol), lit.,[22] $[\alpha]_D^{22}$ −40.3° (neat)}. The optical yield, 91%, was calculated by the observed optical rotations and the known maximum rotations of 1-phenylethylamine.

A number of other asymmetric reductions using different reagents and ketone oxime ethers were performed under conditions similar to those described above.

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